REMARKS

Reconsideration is requested.

Claims 24-47 are pending. Claims 43-46 have been withdrawn from consideration.

Claims 1-23, 28-30, 33, 41 and 43-46 have been canceled, without prejudice. Claims 24-27, 31, 32, 34-40 and 42 will be pending upon entry of the present Amendment. Entry of the Amendment is requested to advance prosecution.

The Examiner's following comment relating to the priority claim is not understood and clarification is requested in the event anything further is required:

> "Receipt is as previously acknowledged of papers (EP 0229 187 18; 7/24/02) submitted less than 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file." See page 2 of the Office Action dated May 28, 2008 (emphasis added).

The BIB DATASHEET indexed in the PTO IFW on May 28, 2008 and Notice of Acceptance dated September 14, 2005 acknowledge receipt of the priority document by the Patent Office.

The Section 112, second paragraph, rejection of claims 37 and 38 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The Examiner explains the rejection as follows:

> "Claims 37 and 38 recite "wherein the transposable nucleic acid comprises, flanked by two inverted repeats, the target polynucleotide. .." which is not clear and renders the claim indefinite. Claim 36 from which claim 37 depends on recite "the target polynucleotide construct comprises a transposable nucleic acid construct". However, Claim 37

> seems to recite "the transposable nucleic acid comprises "...the target polynucleotide construct" [sic]. Thus, one of ordinary skill in the art would not be able to determine with [sic] element(s) is/are comprised by the claimed "transposable nucleic acid." See page 4 of the Office Action dated Mary 28, 2008

The quoted passage of Claim 37, which appears to be the basis for the rejection, was amended however in an Amendment filed January 18, 2008. The Examiner appears to be relying on a previous version of the claims as a basis for the rejection. The pending version of Claims 37 and 38 presented above are believed to be definite. Withdrawal of the Section 112, second paragraph, rejection of claims 37 and 38 is requested.

To the extent not obviated by the above amendments, the Section 102 rejection of claims 24-29, 35, 39, 41, 42 and 47 over Rondon (Applied and Environmental Microbiology, Vol. 66(6):2541-2547) "as evidenced by" Rondon (PNAS, Vol. 96: 6451-6455, 1999), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following distinguishing comments.

The applicants submit that Rondon describes a method for producing and analysing an environmental DNA library comprising:

cloning environmental DNA into BAC vectors;

screening this library to phenotypically select vectors comprising cloned polynucleotides encoding a particular biochemical activity;

identifying the locus responsible for said activity by insertional inactivation via transposon mutangenesis; and

sub-cloning the identified gene to control its function.

Consequently, Rondon et al. fails to teach several elements of the claimed invention, as further detailed below.

The applicants submit that Rondon et al fails to teach the insertion of a target polynucleotide construct into selected cloning vectors in a region distinct from the polynucleotide having a particular characteristic.

In order to achieve an insertional inactivation, the target polynucleotide construct, which is in Rondon et al. a transposon, has to be inserted into the polynucleotide having a particular characteristic.

The applicants submit that Rondon et al does not disclose a target polynucleotide construct comprising nucleic acids encoding an origin of transfer and an integrase.

The target polynucleotide construct (i.e. the transposon) used to mutagenize the BAC vector library in Rondon et al. is Tn*PhoA* which only comprises inverted repeats, a multi-cloning site, an antibiotic encoding gene and the *PhoA* gene encoding a bacterial phosphatase (Manoil and Beckwith, Proc Natl Acad Sci U S A. 1985 Dec;82(23):8129-33).

The cited reference fails to teach the integration of said modified vectors (i.e. BAC vectors comprising the transposon into the polynucleotide having a particular characteristic) into the chromosome of the recipient host cell. In recipient host cells as described in Rondon, BAC vectors are maintained in a replicative episomic form.

Consequently, Rondon et al fails, at a minimum, to teach steps (ii), (iii) and (iv) of the method of the presently claimed invention.

Withdrawal of the Section 102 rejection is requested.

To the extent not obviated by the above amendments, the Section 102 rejection of claims 24, 27, 28, 33 and 35 over Haldimann (Journal of Bacteriology, Vol. 183(21):6384-6393 (2001)), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following distinguishing comments.

This cited reference is understood by the applicants to describe CRIM plasmids which can be used for the construction of gene libraries and comprises:

a polylinker or a cloning region;

a phage attachment site;

a conditional-replication origin; and

a selectable marker.

These plasmids can be integrated into the chromosome of Escherichia coli and related bacteria by site-specific recombination at a phage attachment site. This integration requires the use of a *Int* helper plasmid supplying a phage integrase.

The applicant respectfully submits that the cited art fails to teach each and every aspect of the claimed invention. Consideration of the following in this regard is requested.

The applicants submit that Haldimann does not relate to a method of analysing a library of polynucleotide as presently claimed but only to plasmids which may be possibly used to achieve this library. Consequently, this article does not literally teach steps (i) and (iv) of the claimed invention.

Moreover, the applicants submit that Haldimann fails to teach the insertion of a target polynucleotide construct into CRIM vectors comprising nucleic acids encoding an

origin of transfer and an integrase as presently claimed. In fact, plasmids described Haldimann do not comprise any origin of transfer and the integrase is supplied by using a helper plasmid.

Consequently, the claims are submitted to be patentable over Haldimann et al., and withdrawal of the Section 102 rejection based on the same is requested.

To the extent not obviated by the above amendments, the Section 103 rejection of claims 24-32, 35, 39-42 and 47 have been rejected as allegedly being obvious over Rondon in view of Chain (Journal of Bacteriology, Vol. 182: 5486-5494); the Section 103 rejection of claims 24-35, 39-42 and 47 over Rondon, Chain and Groth (PNAS, Vol. 97:5995-6100, 2000); and the Section 103 rejection of claims 24-42 and 47 over Rondon, Chain, Groth, Berg (PNAS, Vol. 79; 2632-2635, 1982) and Devine (U.S. Patent No. 5,728,551) are traversed. Reconsideration and withdrawal of the rejections are requested in view of the above and the following distinguishing comments.

The present invention

The present invention relates to a method of analysing a polynucleotide library relying on the modification of selected cloning vectors containing a polynucleotide having a particular characteristic in order to allow their transfer in a selected recipient host cell and their integration, or at least the integration of the polynucleotide having a particular characteristic, into the chromosome of said selected recipient host cell. The analysis of the polynucleotide having a particular characteristic is then achieved by determining the phenotype or properties of the selected recipient host cell containing said polynucleotide into its chromosome.

This method allows testing the expression of the activity exhibited by the polynucleotide having a particular characteristic in different expression systems, i.e., different selected recipient host cell, by providing a stable expression and maintenance in said systems thanks to the integration of the polynucleotide in a chromosome of said selected recipient host cell.

This method thus allows one to overcome expression problems of the activity coded by the polynucleotide having a particular characteristic such as transcription, translation/post-translation problems or lack of essential partners of chain reaction by changing the host cell, or even deletion of the polynucleotide having a particular characteristic by integration into the chromosome of the host cell.

Rondon

The deficiencies of Rondon et al. are described above. The secondary references are not believed to cure the deficiencies of Rondon et al.

Chain, Groth, Berg and Devine

Chain et al. relates to a method for cloning large fragment of bacterial genomic DNA comprising

inserting two parallel copies of *oriT* and a plasmid replication origin into the targeted chromosome;

supplying transfer genes in *trans* to specifically transfer the *oriT*-flanked region in *E. coli,* wherein the inserted replication origin is functional;

maintaining this plasmid in an episomic form in *E. coli.*

Groth et al. describes the use of the ΦC31 integrase to operate site specific unidirectional integrations into the genome of the host cell.

Berg et al. describes fundamental principles of the use of transposon elements in molecular biology, i.e., inverted repeats, transposase and marker gene (antibiotic resistance).

Devine et al. relates to a method for providing templates for DNA sequencing using artificial transposons.

Examiner's combination of cited documents

The Examiner's combinations of cited art would not have made the claimed invention obvious. Consideration of the following in this regard is requested.

Firstly, the applicants submit that that aim of the method disclosed in Chain et al. is different from the aim of the method of Rondon et al. or of the present invention.

Chain et al. only relates to a method for cloning a fragment of bacterial chromosomic DNA into a plasmid and maintaining obtained plasmid in an episomic form in a recipient cell (i.e., from chromosome to vector).

On the contrary, the presently claimed invention relates to a method of analysing a library of polynucleotides relying on the integration of selected cloning vectors and/or the contained polynucleotide having a particular characteristic into a chromosome of a selected recipient host cell (i.e., from vector to chromosome).

The other three documents, Groth et al., Berg et al. and Devine et al, describe the use of phage integrases and transposons to modify DNA constructs.

At the time of the present invention, the properties and the use of these elements were known by the ordinarily skilled person and these documents do not teach or suggest the use of these elements in a method of analysing a polynucleotide library.

Consequently, the applicants believe that none of these documents, Chain et al., Groth et al., Berg et al. and Devine et al., relate to a method of analysing a polynucleotide library and the ordinarily skilled person would not have been motivated by the cited art, at the time of the invention, to combine these documents with Rondon et al. to have made the claimed invention.

The applicants note that the teachings of the cited art must be taken as a whole, and that the basis of the Section 103 rejections appears to have been made be made on improper hindsight reconstruction.

Rondon and Chain

As discussed above, Rondon et al fails to teach

the insertion of a target polynucleotide construct into selected cloning vectors in a region distinct from the polynucleotide having a particular characteristic;

the insertion of a target polynucleotide construct comprising nucleic acids encoding an origin of transfer and an integrase; and

the integration of cloning vectors modified by the insertion of said target polynucleotide construct and/or of the polynucleotide having a particular characteristic into the chromosome of the recipient host cell in order to determine the phenotype or properties of the selected recipient host cell containing said polynucleotide

Chain et al. relates to a method for cloning large fragment of bacterial chromosomic DNA by inserting two parallel copies of *oriT* into bacterial chromosomic DNA to extract the flanking region into a vector.

Therefore, this document does not teach or suggest insertion of "target polynucleotide construct", comprising an *oriT*, into a cloning vector containing a polynucleotide having a particular characteristic.

Consequently, Chain et al. fails to teach or suggest the insertion of a target polynucleotide construct into selected cloning vectors in a region distinct from the polynucleotide having a particular characteristic.

Furthermore, as noted by the Examiner page 11 of the Office Action dated May 28, 2008, "the combination of Rondon et al. and Chain et al does not explicitly teach the target polynucleotide construct comprises an integrase" (emphasis added).

Moreover, the applicants submit that in Chain et al., the plasmid obtained by site specific recombination at the *OriT* sites is transferred in a recipient host cell and maintained in an episomic form. Thus, this document fails to suggest the integration of cloning vectors modified by the insertion of a target polynucleotide construct into a chromosome of a recipient host cell.

Consequently, this Chain et al fails to cure the deficiencies of Rondon et al. noted above.

Rondon, Chain, Groth, Berg and Devine

Groth et al., Berg et al. and Devine et al, are understood to describe the use of phage integrases and transposons to modify DNA constructs.

As with Chain et al., the applicants submit that these documents do not relate to a method for analysing a library of polynucleotide. Consequently, they do not teach or suggest the insertion of "target polynucleotide construct" into a selected cloning vector containing a polynucleotide having a particular characteristic and thus fail to teach the insertion of a target polynucleotide construct into selected cloning vectors in a region distinct from the polynucleotide having a particular characteristic.

Consequently, these documents fail to cure the deficiencies of Rondon and Chain et al., noted above.

The claims are submitted to be patentable over the cited combinations of art and withdrawal of the Section 103 rejections is requested.

The claims are submitted to be in condition for allowance and entry of the present Amendment and a Notice of Allowance are requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required in this regard.

Respectfully submitted,

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